

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Havelund et al

Application No.: To be assigned

Group Art Unit: To be assigned

Filed: February 25, 2002

Examiner: To be assigned

For: Aggregates of Human Insulin Derivatives

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, DC 20231

Sir:

Before the above-captioned application is taken up for examination, entry of the following amendment is respectfully requested:

IN THE CLAIMS:

Please cancel claims 1-60 without prejudice.

Please add the following claims:

61. A water-soluble aggregate of an insulin derivative having a lipophilic substituent linked to a lysine residue optionally through an amino acid linker, wherein the lipophilic substituent is selected from the group consisting of 5- α lithocholic acid and 5- β lithocholic acid, and wherein the aggregate (a) has a size larger than aldolase, (b) comprises 2 to 5 zinc ions per 6 molecules of insulin derivative, and (c) is formed in an environment having an ionic strength and pH of the tissue after subcutaneous injection.
62. A water-soluble aggregate according to claim 61, wherein said aggregate has a size larger than ferritin.
63. A water-soluble aggregate according to claim 61, wherein said aggregate has an apparent volume corresponding to a K_{AV} value of less than 0.32 as determined by gel filtration using a Sephacryl[®] S-300 HR gel.

64. A water-soluble aggregate according to claim 61, wherein said aggregate has an apparent volume corresponding to a K_{AV} value of less than 0.20 as determined by gel filtration using a Sephacryl® S-300 HR gel.
65. A water-soluble aggregate according to claim 61, wherein said aggregate has an apparent volume corresponding to a K_{AV} value of less than 0.50 as determined by gel filtration using a Superose® 6HR gel.
66. A water-soluble aggregate according to claim 61, wherein said aggregate has an apparent volume corresponding to a K_{AV} value of less than 0.40 as determined by gel filtration using a Superose® 6HR gel.
67. A water-soluble aggregate according to claim 61, wherein said aggregate is soluble at a pH in the range of 6.8 to 8.5.
68. A water-soluble aggregate according to claim 61, wherein the lipophilic substituent is linked to the lysine residue through an amino acid linker.
69. A water-soluble aggregate according to claim 68, wherein the amino acid linker is selected from the group consisting of α -glutamyl, γ -glutamyl, β -aspartyl and α -aspartyl.

Claims 1-60 have been canceled without prejudice or disclaimer. Claims 61-69 have been added. Therefore, claims 61-69 are pending in the present application.

Claims 61-62 find support inter alia on page 5, lines 2-4 and 26-28, on page 8, lines 4-5 and 11-12, and on page 11, lines 6-10; claims 63-66 find support on page 5, lines 5-8; claim 67 finds support on page 5, line 9; and claims 68-69 find support on page 8, lines 18-22.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: February 25, 2002

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